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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/486,480	10/25/2000	James A. Spudich	18557A-00021	9741

7590 12/13/2002

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	12

DATE MAILED: 12/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/486,480	Spudich et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 18, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-55* ~~is~~/are pending in the application.

4a) Of the above, claim(s) *14-55* ~~is~~/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-12* ~~is~~/are rejected.

7) ☒ Claim(s) *13* is/~~are~~ objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Oct 25, 2000* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5.*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 07/23/02 (paper no. 8). With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election, without traverse, filed 09/18/02 (paper no. 11) of invention IV, claims 1-13, in response to the lack of unity mailed 06/19/02 (paper no. 6).

Status of Claims

3) Claims 1-55 are pending.

Claims 14-55 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1-13 have been elected via the election filed 09/18/02.

Claims 1-13 are under examination. A First Action on the Merits is issued for these claims.

Sequence Listing

4) The raw sequence listing submitted in the instant application has been entered on 08/02/02 (paper no. 9).

Priority

5) The instant application is a national stage 371 application of PCT/US98/18531, filed 09/03/1998 and claims priority to the US provisional application, 60/057,929, filed 09/04/1997.

Information Disclosure Statement

6) Acknowledgment is made of Applicants' information disclosure statement filed 08/27/01 (paper no. 5). The information referred to therein has been considered and a signed copy is attached to this Office Action (paper no. 12).

Drawings

7) The drawings submitted in the instant application are not objected to by the Draftsperson under 37 C.F.R 1.84 or 1.152 and as such, the drawings have been approved as formal drawings.

Abstract

8) This application currently does not contain an abstract of the disclosure as required by 37

C.F.R 1.72(b). However, as this application is a 371 of application of PCT/US98/18531, a copy of the published abstract from this application is placed in the instant application as page number 42. If Applicants desired changes to the abstract, such changes should be directed to the abstract of the application, PCT/US98/18531.

Specification - Informalities

9) The specification is objected to for the following reason(s):

(a) The first paragraph of the specification does not accurately reflect the priority information, as indicated above under 'Priority'. Correction is requested.

(b) The use of the trademark in the instant specification has been noted in this application. For example, see page 35, line 22: "Triton X-100". The recitation should be capitalized wherever it appears and be accompanied by the generic terminology. Each letter of the trademark must be capitalized. See M.P.E.P 608.01(V) and Appendix l. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to trademark recitations, wherever such recitations appear. (c) The recitation 'application USSN ___/___,___" at line 5 of page 28 of the specification appears to be incomplete.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

10) Claims 6 and 7 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 6 lacks proper antecedence or has improper antecedence in the recitation: "said layered silicate" (see lines 2 and 3). Claim 6 depends from claim 1, which recites "a layered silicate surface", but not "a layered silicate".

(b) Claim 7 has improper antecedence for the recitation: "said sodium salt" (see line 1). Claim 7 depends from claim 1 (not from claim 6), which does not recite any sodium salt.

Rejection(s) under 35 U.S.C. 103

11) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a)** A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

12) Claims 1 and 4-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hirabayshi *et al.* (*J. Mol. Recog.* 3: 204-207, 1990) (Hirabayashi *et al.*, 1990) in view of Mueller *et al.* (*Biophys. J.* 68: 1681-1686, 1995).

Hirabayashi *et al.* (1990) taught a method of immobilizing a biological molecule, such as, a recombinant human beta-galactosidase-binding lectin, to an agarose substrate by fusing or covalently attaching the lectin to an arginine tail (i.e., tag) at the C-terminus and contacting the resultant arginine-tagged lectin with the agarose substrate or surface in 50 mM sodium acetate buffer. The arginine tail consists of a single arginine (see abstract; and sections 'Experimental Procedure' and 'Results').

Hirabayashi *et al.* do not teach the use of mica in their method.

However, Mueller *et al.* taught that it was conventional to use mica as an alternative substrate for attaching a biomolecular moiety thereon via a polyamino acid tag. See abstract; page 1683; and 'Materials and Methods'.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Hirabayashi's (1990) agarose substrate with Mueller's mica to produce the instant invention with a reasonable expectation of success. Given the routine and

conventional use of mica for attaching a biomolecular protein as taught by Mueller *et al.*, substitution of one substrate with another, alternative, art-known substrate which has already been used in the art for attaching a biomolecule would have been obvious to one of skill in the art, would have been well within the realm of routine experimentation and would have brought about similar results, absent evidence to the contrary.

Claims 1 and 4-12 are *prima facie* obvious over the prior art of record.

13) Claims 1-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hirabayshi *et al.* (*J. Chromatogr.* 597: 181-187, 1992 - Applicants' IDS) (Hirabayashi *et al.*, 1992) in view of Mueller *et al.* (*Biophys. J.* 68: 1681-1686, 1995).

Hirabayashi *et al.* (1992) taught an advantageous method of using an arginine tag to attach a moiety, such as a target protein, lectin or a sugar, to a resin substrate. The arginine tag is fused (i.e., covalently attached or conjugated) to the protein (see Figure 1; sections 'Experimental' and 'Results'). The arginine-tailed lectin moiety is contacted with a 50 mM solution of sodium acetate (see second full paragraph in the right column on page 182). The arginine tag is introduced at the C-terminus of a recombinant protein by mutagenesis (see paragraph bridging pages 181 and 182; and section 'Experimental'). Hirabayashi *et al.* taught the advantages of arginine-tail method over the previous affinity tag procedures in that only a single arginine or three-arginine (i.e., polyarginine consisting of only arginine residues) tag has minimum or no effect on protein or sugar functions (see paragraph bridging pages 186 and 187). Hirabayashi *et al.* (1992) taught that the use of arginine tags provides an alternative affinity tag procedure because of its simplicity, applicability and harmlessness (see left column on page 187).

Hirabayashi *et al.* (1992) do not teach the use of mica in their method.

However, Mueller *et al.* taught that it was conventional to use mica as an alternative substrate for attaching a biomolecular moiety via a polyamino acid tag. See abstract; page 1683; and 'Materials and Methods'.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Hirabayashi's (1992) resin substrate with Mueller's mica to produce the instant invention with a reasonable expectation of success. Given the routine and conventional use of mica for attaching a biomolecular protein as taught by Mueller *et al.*, substitution of one

substrate with another, alternative, art-known substrate which has already been used in the art for attaching a biomolecule would have been obvious to one of skill in the art, would have been well within the realm of routine experimentation and would have brought about similar results, absent evidence to the contrary.

Claims 1-12 are *prima facie* obvious over the prior art of record.

14) Claims 1-5, 8 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mueller *et al.* (*Biophys. J.* 68: 1681-1686, 1995) in view of Hirabayshi *et al.* (*J. Chromatogr.* 597: 181-187, 1992 - Applicants' IDS) (Hirabayashi *et al.*, 1992).

Mueller *et al.* taught a method of adsorbing purple membranes (i.e., moieties, biomolecules or proteins) to mica via polylysine (i.e., tag). See abstract; page 1683; and 'Materials and Methods'.

Mueller *et al.* do not teach the use of an arginine tag in their method.

However, Hirabayashi *et al.* (1992) taught the advantageous use of an arginine tag to attach a moiety, such as a target protein, lectin or a sugar to a resin substrate. The arginine tag is fused (i.e., covalently attached or conjugated) to the protein (see Figure 1; sections 'Experimental' and 'Results'). The arginine-tailed lectin moiety is contacted with a 50 mM solution of sodium acetate (see second full paragraph in the right column on page 182). The arginine tag is introduced at the C-terminus of a recombinant protein by mutagenesis (see paragraph bridging pages 181 and 182; and section 'Experimental'). Hirabayashi *et al.* taught the advantages of arginine-tail method over the previous affinity tag procedures in that only a single arginine or three-arginine (i.e., polyarginine consisting of only arginine residues) tag has minimum or no effect on protein or sugar functions (see paragraph bridging pages 186 and 187). Hirabayashi *et al.* (1992) taught that the use of arginine tags provides an alternative affinity tag procedure because of its simplicity, applicability and harmlessness (see left column on page 187).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Mueller's polylysine tag with Hirabayashi's arginine tag to produce the instant invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of having an alternative affinity tag that is advantageous due to its simplicity and applicability as taught by Hirabayshi *et al.* (1992). Given the routine and conventional use of a polyarginine tag for attaching a target protein to

a substrate as taught by Hirabayshi *et al.* (1992), substitution of one affinity tag with another, alternative, art-known affinity tag which has already been used in the art for attaching a target protein to a substrate would have been obvious to one of skill in the art, would have been well within the realm of routine experimentation and would have brought about similar results.

Claims 1-5, 8 and 9 are *prima facie* obvious over the prior art of record.

15) Claims 1-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sassenfeld *et al.* (*Biotechnol.*2: 76-81, 1984) in view of Geke *et al.* (*J. Colloid and Interface Science* 189: 283-287, 15 May 1997- already of record).

Sassenfeld *et al.* taught a method of attaching, conjugating or fusing a moiety or recombinant biomolecule, such as, human urogastrone having a C-terminal polyarginine (i.e., tag) for use in ion-exchange purification (see abstract) and contacting the polyarginine tagged-urogastrone with an ion-exchange resin substrate in a solution containing a sodium salt in a concentration of at least 1 mM (see page 77, especially under 'Results'). The polyarginine is attached at the carboxyl terminus of the urogastrone and comprises about five arginine residues (see page 77, column bridging left and right columns).

Sassenfeld *et al.* do not teach the use of a layered silicate or a mica substrate in their method.

However, the use of mica in ion exchange was well known in the art at the time of the instant invention. For instance, Geke *et al.* taught the use in ion exchange of a layered silicate, such as, mica as a particularly attractive substrate with its molecularly flat surface (see title; abstract; second paragraph under section I; and sections II and III). Geke *et al.* further taught that ion exchange on mica offers a sensitive new experimental method (see 'Conclusions').

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Sassenfeld's substrate with Geke's layered silicate, such as, mica to produce the instant invention with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of having a new sensitive method, since Geke *et al.* expressly taught that ion exchange on particularly attractive substrate, such as, mica offers a sensitive new experimental method. Substitution of one ion exchange substrate with another, alternative, art-known ion exchange substrate would have been obvious to one of skill in the art, would have been well within the realm of routine experimentation

and would have brought about similar results.

Claims 1-12 are *prima facie* obvious over the prior art of record.

Relevant Prior Art

16) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Kallury *et al.* (US 5,405,766 - already of record) taught the advantages of using inorganic, granular silica for chromatographic purposes due to its resistance to acids and organic solvents and to microbial attack in addition to their rigidity, thermal stability and outstanding hydrodynamic properties (see first paragraph in column 14).

- Hirabayashi *et al.* (*J. Mol. Recog.* 3: 204-207, 1990) (Hirabayashi *et al.*, 1990) expressly suggested that it is possible to add a longer tail terminated with arginine if necessary in order to increase binding affinity or hydrophilicity (see page 207, left column). The method is advantageous in terms of generality and minimal effect on both structure and function of the target protein due to the addition of a single, hydrophilic arginine residue (see page 207, left column).

- Nova *et al.* (US 6,319,668) taught agarose, silica and mica to be natural support matrices that are used in the art of chromatography to immobilize ligands and other biomolecules including proteins (see section A in column 27 and section 1 in column 32).

Remarks

17) Claims 1-12 stand rejected.

Claim 13 is objected for being dependent from a rejected claim. The subject matter of claim 13 is free of prior art currently of record.

18) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December, 2002

S. DEVI, PH.D.
PRIMARY EXAMINER